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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,709	05/17/2005	Jean-Marc Balloul	017753-190	3092

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/500,709	BALLOUL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 2, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence search alignment*.

DETAILED ACTION

This Office Action is a response to Applicant's Preliminary Amendment filed September 23, 2004.

Claims 1-33 have been canceled. New claims 34-41 are acknowledged.

Claims 34-41 have been examined on the merits.

Information Disclosure Statement

Applicant's information disclosure statement filed July 2, 2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Priority

It is noted that the instant application is the national stage entry of PCT/FR03/00007, filed January 3, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-36 are indefinite because they recite the limitations, "said oligonucleotide". There is insufficient antecedent basis for these limitations in the claims because claim 34, for which claims 35 and 36 depends, recites "nucleic acid", not "oligonucleotide". Appropriate correction is required.

Claim 34 is also indefinite because the term "CSF-1" is not clearly defined. Since abbreviations often have more than one meaning, it is suggested that inserting the full name of the stimulating factor would overcome the instant rejection. It is noted that claims 37-41 are included in this rejection because of their dependency therein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Claim 41 is drawn to a method for the treatment of cancer in a subject comprising administering a therapeutically effective amount of a combination product comprising (i)

at least one substance capable of inhibiting CSF-1 activity and/or at least one nucleic acid, comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity, and (ii) at least one substance having at least a cytotoxic activity and/or at least one nucleic acid, comprising at least one sequence coding for a substance having at least a cytotoxic activity. It is noted that the Examiner is interpreting the nucleic acid, comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity of Applicant's invention to be an antisense or ribozyme nucleic acid.

The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Although the breadth of the elected invention is rather narrowly drawn to a method for the treatment of cancer in a subject comprising administering a therapeutically effective amount of a combination product comprising a nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity, the nature of the invention relies upon the use of nucleic acid therapeutics in the whole animal (i.e. *in vivo*). While the level of one of ordinary skill practicing the instant invention would be high, the level of predictability is considered to be extremely variable as evident in the prior art (discussed in detail below), and is not considered to provide,

in and of itself, sufficient enablement to practice the invention as claimed. Moreover, the amount of direction provided by the inventor (also discussed below) is similarly lacking, since the disclosed guidance depends explicitly, and almost entirely, on the teachings of the prior art. There are no working examples of the invention as instantly claimed. The quantity of experimentation needed to make or use the invention based on the content of the disclosure alone is therefore not enabling for practice of the instant invention *in vivo*.

The specification teaches that antisense oligonucleotides targeted to and specifically hybridizable to human CSF-1 (SEQ ID NO:1) inhibited CSF-1 gene expression in human breast cancer cells in culture (*in vitro*). The specification references prophetic methods of a method for the treatment of cancer in a subject comprising administering a therapeutically effective amount of a combination product comprising a nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity. Such methods of treatment are not exemplified, and thus rely exclusively upon the state of the prior art in order to provide enablement.

Regarding the state of the prior art, a thorough review of the field clearly indicates that inhibition of gene expression and/or activity utilizing oligonucleotide therapeutics *in vitro* is routine. However, *in vivo* inhibition of gene expression and/or activity at the time of Applicant's filing and even to the present time is not routine for several reasons, primarily due to the problem of delivery, and to a lesser extent, specificity and length of bioactivity of the oligonucleotide therapeutic. The problem of delivery results from the poor ability of nucleic acid therapeutics to reach the appropriate

target cell, and penetrate the membrane (or membranes, since they are typically taken into lysosomes) in sufficient concentrations such that the target gene is inhibited to a degree necessary to result in a therapeutic effect.

The following references are cited herein to illustrate the state of the art in support of these statements.

For example, Jen et al. (Stem Cells 2000, Vol. 18, pages 307-319) indicates, "[O]ne of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable...Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive".

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pages 503-514) states, "It is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA". From column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have

indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

A recent (2002) review article by Braasch et al. (Biochemistry, Vol. 41, pages 4503-4510) concludes that major obstacles persist in the art of using nucleic acid therapeutics in treating disease: "[G]ene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (see page 4503, paragraphs 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism".

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (see page 4503, paragraphs 1 and 2). Branch, A. (TIBS, 1998 Vol. 23, pages 45-40) adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which

render most potential binding sites inaccessible to antisense molecules" (see page 45, third column).

Branch et al. discuss the problems pertaining to non-specific oligonucleotide interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs. These effects must be explored on a case by case basis" (see page 50), while Tamm et al. (The Lancet, 2001 Vol. 358 pages 489-497) states that, "[I]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (see page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that, "In fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain

consistent therapeutic benefit "(see page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that, "[I]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the specification which depends solely upon the state of the prior art would not enable claims directed to the *in vivo* use of nucleic acids such as antisense nucleic acids, let alone claims directed to their therapeutic use *in vivo*, because, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* is highly unpredictable. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification.

The specification as filed teaches that antisense oligonucleotides targeted to and specifically hybridizable to human CSF-1 (SEQ ID NO:1) inhibited the gene expression of CSF-1 in human breast cancer cells in culture (*in vitro*). The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed nucleic acids or methods of using said nucleic acids

in *in vivo* environments, because the specification teaches only prophetic methods of treating cancer in a subject using a combination product comprising a nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity. The specification does not teach any specific treatment regimen that is specific for the nucleic acid, but rather relies upon the guidance of the prior art in enabling one of skill to practice the instantly claimed methods of cancer treatment.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed combination product comprising a nucleic acid, comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity in methods in *in vivo* environments. Thus, although the specification prophetically considers and discloses general methodologies of using the nucleic acids *in vivo* or in methods of treating cancer in a subject, such a disclosure would not be considered enabling since the state of nucleic acid, particularly antisense-mediated gene inhibition, is highly unpredictable.

In order to practice the claimed invention *in vivo* in a subject, a number of variables would have to be optimized, including 1) the form of the antisense nucleic acid, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 2) the mode of delivery of the antisense nucleic acid to an subject that would allow it to reach the targeted cell, 3) the amount of antisense nucleic acid that would need to be delivered in order to treat cancer, and 4) ensuring the antisense nucleic acid remains viable in a cell for a period of time that allows a measurable and significant therapeutic effect. Each one of these variables would have to be empirically

determined for each nucleic acid, comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity claimed. While optimization of any single one of these steps may be routine, when taken together, the amount of experimentation required becomes such that one of skill in the art could not practice the invention without undue, trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Birchenall-Roberts et al. (Journal of Immunology, 1990 Vol. 145:3290-3296, made of record on Applicant's information disclosure statement filed July 2, 2004).

Claim 34 is drawn to a combination product comprising (i) at least one substance capable of inhibiting CSF-1 activity and/or at least one nucleic acid, comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity, and (ii) at least one substance having at least a cytotoxic activity and/or at least one nucleic acid, comprising at least one sequence coding for a substance having at least a cytotoxic activity. Claim 40 is dependent on claim 34 and includes all the limitations of claim 34 with the further limitation wherein the combination product further comprises a

pharmaceutically acceptable vehicle.

Birchenall-Roberts et al. disclose antisense oligomers and antibodies to CSF-1 (see page 3291, first column). Specifically, Birchenall-Roberts et al. disclose the use of these factors together, inhibits the growth of an established line of monocyte cells *in vitro* (see Figure 5). It is noted that the Examiner is interpreting the CSF-1 antisense disclosed by Birchenall-Roberts et al. to be the substance capable of inhibiting CSF-1 activity as claimed in Applicant's invention. It is further noted that the Examiner is interpreting the CSF-1 monoclonal antibody disclosed by Birchenall-Roberts et al. to be the substance having at least a cytotoxic activity as claimed in Applicant's invention. Regarding the pharmaceutically acceptable vehicle as claimed in Applicant's invention, Birchenall-Roberts et al. disclose the cultured monocyte cells were cultured in conditioned media prior to and during exposure to antisense oligomers and antibodies to CSF-1. The Examiner is interpreting the conditioned media disclosed by Birchenall-Roberts et al. to be a pharmaceutically acceptable vehicle.

Therefore Birchenall-Roberts et al. anticipate claims 34 and 40.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-37, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. [U.S. Patent No. 5,959,097].

Claims 34 and 40 are drawn to a combination product comprising (i) at least one substance capable of inhibiting CSF-1 activity and/or at least one nucleic acid, comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity, and (ii) at least one substance having at least a cytotoxic activity and/or at least one nucleic acid, comprising at least one sequence coding for a substance having at least a cytotoxic activity, characterized in that the nucleic acid is selected from the group of oligonucleotides capable of hybridizing at the region between the nucleotide in position 135 and the nucleotide in position 152 inclusive of SEQ ID NO:1, and a pharmaceutically acceptable vehicle thereof. Claims 35-37 and 39 are dependent on claim 34 and include all the limitations of claim 34 with the further limitations characterized in that oligonucleotide comprises 8 to 30 nucleotides; characterized in that the oligonucleotide comprises 12 to 25 nucleotides; characterized in that the substance having at least a cytotoxic activity is selected from the substances of spindle agents; and characterized in that the substance having at least a cytotoxic activity is selected from a protein coded by a suicide gene.

Monia et al. teach antisense oligonucleotides that are targeted to and specifically

hybridizable to nucleic acids encoding MEK2. Specifically, Monia et al. teach and claim an antisense oligonucleotide targeted to MEK2 with the following sequence:

5'-acgcagggagcccggcca-3' (see SEQ ID NO:42 and claims 11 and 12). It is noted that this antisense oligonucleotide is almost 100% complementary to nucleotides 148-163 of SEQ ID NO:1 of the instant invention, as it has only one mismatch (see attached sequence alignment). Since this antisense oligonucleotide is almost fully complementary to nucleotides 148-163 of SEQ ID NO:1 of the instant invention, containing only one mismatch, it meets the structural limitations of the claimed invention and would be expected to be capable of hybridizing at the region between the nucleotide in position 135 and the nucleotide in position 152 inclusive of SEQ ID NO:1 since the instant specification at page 8, third full paragraph teaches, "[T]hose skilled in the art know that it is not necessary for 100% of nucleotides comprising an oligonucleotide to be complementary to nucleotides in the target sequence, for hybridization to occur." Accordingly, SEQ ID NO:42, the antisense oligonucleotide targeted to MEK2 disclosed by Monia et al. would be expected to be capable of hybridizing at the region between the nucleotide in position 135 and the nucleotide in position 152 inclusive of SEQ ID NO:1 as claimed.

The burden of establishing whether the prior art oligonucleotide is capable of inhibiting CSF-1 activity, under generally any assay condition, falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been

established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that SEQ ID NO:42, the antisense oligonucleotide targeted to MEK2 disclosed by Monia et al. would or would not have the additional functional limitation of being capable of inhibiting CSF-1 activity as instantly claimed.

Monia et al. also teach the antisense oligonucleotides of their invention are comprised in pharmaceutically acceptable carriers and are combined with chemotherapeutic agents which function by a non-antisense mechanism (see, for example, columns 10-12 and column 24, second full paragraph). For example, Monia et al. teach the antisense oligonucleotides of their invention are combined with vincristine or vinblastine, which are spindle agents as claimed in claim 37 of the instant invention (see, for example, column 24, second full paragraph). Monia et al. also teach the antisense oligonucleotides of their invention are combined with acyclovir and

ganciclovir which code for proteins of suicide genes as claimed in claim 39 of the instant invention (see, for example, column 24, second full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to make a combination product comprising at least one nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity and at least one substance having at least a cytotoxic activity using the teachings of Monia et al. It would have been obvious to have the nucleic acid comprise 8 to 30 nucleotides or 12 to 25 nucleotides using the teachings of Monia et al.

One of ordinary skill in the art, at the time of Applicant's filing, would have been motivated to make a combination product comprising at least one nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity and at least one substance having at least a cytotoxic activity, including spindle agents or proteins coded by suicide genes since Monia et al. taught antisense oligonucleotides, combined with other chemotherapeutic agents which function by a non-antisense mechanism, are useful for combination therapy. One of ordinary skill in the art would have been motivated to have the nucleic acid comprise 8 to 30 nucleotides or 12 to 25 nucleotides since this is a conventional size for optimal binding of a gene of interest and for ease of synthesis and delivery to cells in culture (see, for example, Monia et al. at Table 1). One or ordinary skill in the art would have been motivated to make the combination product comprising at least one nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity and at least one substance having at least a cytotoxic activity, further comprising

a pharmaceutically acceptable vehicle for the purpose of delivery to cells *in vivo* as taught by Monia et al.

One of ordinary skill in the art would have expected success at making a combination product comprising at least one nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity and at least one substance having at least a cytotoxic activity, since Monia et al. detailed how to make and design such combination products. One of ordinary skill in the art would have expected success at making a combination product comprising at least one nucleic acid comprising at least one sequence coding for a substance capable of inhibiting CSF-1 activity and at least one substance having at least a cytotoxic activity, further comprising pharmaceutically acceptable vehicles since the prior art taught how to successful design such products for use *in vivo* (see Monia et al.).

Therefore, absent evidence to the contrary, the invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
December 6, 2006

Sequence search alignment...

iss.res

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RESULT 228
US-09-197-378-42/c
; Sequence 42, Application US/09197378
; Patent No. 5959097

; GENERAL INFORMATION:
;  APPLICANT: Brett P. Monia
;  APPLICANT: Lex M. Cowsert
;  TITLE OF INVENTION: ANTISENSE MODULATION OF MEK2 EXPRESSION
;  FILE REFERENCE: RTS-0017
;  CURRENT APPLICATION NUMBER: US/09/197,378
;  CURRENT FILING DATE: 1998-11-20
;  NUMBER OF SEQ ID NOS: 47
; SEQ ID NO 42
;   LENGTH: 18
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Antisense Oligonucleotide
US-09-197-378-42

  Query Match           0.4%;  Score 14.4;  DB 1;  Length 18;
  Best Local Similarity  93.8%;  Pred. No. 1.8e+02;
  Matches   15;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy        148 TGGCTGGGCTCCCTGC 163
              |||| ||||||||||||
Db         18 TGGCCGGGCTCCCTGC 3
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